REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herein.

I. Status Of The Claims And Formal Matters

Claims 25, 27-32, and 34-46 are now pending in the present application. Claims 26 and 33 are cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Specifically, the recitation of claim 26 - which was fairly based on the examples in the present application - was incorporated into claim 25. Additionally, claim 25 has been amended as suggested by the Examiner on page 7 of the Office Action, with minor exceptions and with the exception that part (b) of claim 25 is clarified to recite that expression of adenoviral E1, E2, or E4 genes are under the control of various promoters. The Examiner is thanked for this suggestion. The Examiner is thanked for proposing amendments to the claim language of claims 28, 29, 34, and 43 on page 4 of the Office Action. Claims 28, 29, 34, and 43 have been amended to reflect the Examiner's concerns, without prejudice without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Support for the claim amendments is found throughout the specification and claims as originally presented.

Claims 45 and 46 are presented, but are not in excess of the claims cancelled, and not raise any new issues requiring any further search or examination. Support for claims 45 and 46 can be found, for example, in Example 15. The Examiner is thanked for indicating that claims 43 and 44 are free of the prior art of record. No new matter is added by these amendments. Nor is any new issue presented by these amendments.

It is respectfully submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. The Restriction Requirement Is Noted

The Office Action alleges that newly submitted claim 33 is directed to an invention that is independent or distinct from the invention originally claimed. Claim 33 is allegedly directed

to replication defective adenovirus and therefore improperly depends from claim 25, which is directed to replication competent adenovirus and allegedly excludes replication defective adenovirus.

Although Applicants disagree, in the interest of expediting prosecution, claim 33 has been cancelled.

III. Priority

The Office Action alleges that the currently pending claims are not entitled to the priority date of May 12, 2000, and are instead entitled only to the date of filing the present application, October 30, 2003.

Although Applicants disagree, in the interest of expediting prosecution, the effective filing date of the instant claims may be considered October 30, 2003.

IV. The Rejections Under 35 U.S.C. §112, First Paragraph Are Overcome

Claims 34-44 and 43-44 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims are alleged to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As to the rejection of claims 34-44, the Office Action asserts that these new claims are not fully supported by the specification. Rather, the specification allegedly describes the construction and use of a CRAd that is a modified human adenovirus subtype 5 (hAd5) where the gene encoding the fiber protein of the CRAd has the knob domain coding region replaced with a sequence encoding the knob domain of human Ad3 (hAd3), which overcomes the CAR-dependent infection of hAd5. Moreover, the E1A promoter is allegedly replaced with a VEGF promoter.

Claim 34 has been clarified to recite: A method of reducing tumor burden in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a modified human conditionally replicative adenovirus subtype 5 (hAd5) having greater infectivity in tumor cells than wild-type adenovirus, wherein: the hAd5 contains and expresses a nucleotide sequence encoding a fiber knob domain from an adenovirus subtype 3 thereby providing a pathway to cell binding other than the coxsackie-adenovirus receptor and enhanced infectivity of the conditionally replicative adenovirus in tumor cells over that of wild-type adenovirus, further

wherein the modified conditionally replicative adenovirus contains a deletion of the E1A promoter and insertion of a promoter region selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin, such that replication is more efficient in tumor cells than in most normal cell types.

It is respectfully submitted that the rejection is moot.

Accordingly, reconsideration and withdrawal of the rejection of claims 34-44 under 35 U.S.C. §112, first paragraph are respectfully requested.

As to the rejection of claims 43-44, the Office Action asserts that these new claims are not fully supported by the specification. Rather, the specification allegedly describes a prophetic CRAd that is a modified human adenovirus subtype 5 (hAd5) where the gene encoding the fiber protein of the CRAd has the knob domain coding region replaced with a sequence encoding the knob domain of canine Ad2 (Cad2) allegedly in order to overcome the CAR-dependent infection of hAd5. The Office Action further asserts that it is implied in the specification that the CXCR4 or survivin promoter should replace the E1A promoter.

Claim 43 has been amended to recite: A method of reducing tumor burden in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a modified human conditionally replicative adenovirus subtype 5 (hAd5) having greater infectivity in tumor cells than wild-type adenovirus, wherein: the hAd5 contains and expresses a nucleotide sequence encoding the fiber knob domain of the canine adenovirus type 2 thereby providing a pathway to cell binding other than the coxsackie-adenovirus receptor and enhanced infectivity of the conditionally replicative adenovirus in tumor cells over that of wild-type adenovirus, further wherein the modified conditionally replicative adenovirus contains a deletion of the E1A promoter, and insertion of a tumor-specific promoter from a gene encoding a protein selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin, such that replication is more efficient in tumor cells than in most normal cell types.

It is respectfully submitted that the rejection is moot.

Accordingly, reconsideration and withdrawal of the rejection of claims 43-44 under 35 U.S.C. §112, first paragraph are respectfully requested.

V. The Rejections Under 35 U.S.C. §112, Second Paragraph Are Overcome

Claims 25-33 and 34-44 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claim 34 is further rejected under 35 U.S.C. §112 as having insufficient antecedent basis. Claims 34-44 are rejected as incomplete for omitting essential structural cooperative relationships of elements. Claims 34-44 are also rejected under 35 U.S.C. §112 as incomplete for omitting essential elements.

As to the rejection of claims 25-33 and 34-44 under 35 U.S.C. §112, second paragraph, the Office Action asserts that claim 25 is written in a confusing manner and suggests re-writing the claim as follows: An infectivity-enhanced conditionally replicative adenovirus having:

(a) a modified fiber protein, said fiber protein being encoded by the genome of the adenovirus, wherein the modified fiber protein is:

i) an adenoviral fiber protein modified by the presence of a ligand comprising Arg-Gly-Asp in the HI loop of the fiber protein; or

ii) an adenoviral fiber protein modified by replacement of its fiber knob domain with a fiber knob domain from a different subtype of adenovirus;

whereby the ligand or fiber knob domain provides a pathway to cell binding by the modified conditionally replicative adenovirus other than the coxsackie-adenovirus receptor, and thereby enhances infectivity of the conditionally replicative adenovirus in tumor cells over that of wild-type adenovirus; and

(b) a tumor-specific promoter operably linked to one or more early genes selected from the group consisting of E1, E2 and E4.

Claim 25 has been amended, reciting the claimed subject matter as suggested by the Examiner, with minor variations, and with the exception that part (b) recites: a tumor-specific promoter driving the transcription of a gene encoding a protein selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin, wherein one or more early genes selected from the group consisting of E1, E2 and E4 are operably linked to said promoter. This clarifies that promoter expression is not under the control of adenoviral regulatory elements, but rather that the adenoviral regulatory elements are under control of the promoter.

Accordingly, reconsideration and withdrawal of the rejection of claims 25-33 and 34-44 under 35 U.S.C. §112, second paragraph are respectfully requested.

As to the rejection of claim 34 under 35 U.S.C. §112, the Office Action alleges that there is insufficient antecedent basis for the limitations "the fiber domain" in line 7 and "the fiber knob domain" in line 8. Claim 34 has been amended to recite "a fiber knob domain" in line 7. Further, "the fiber knob domain" in line 8 has been deleted. These amendments render the objection moot.

It is respectfully submitted that the rejection is moot.

Accordingly, reconsideration and withdrawal of the rejection of claim 34 under 35 U.S.C. §112, second paragraph is respectfully requested.

As to the rejection of claims 34-44 under 35 U.S.C. §112, the Office Action asserts that the claims are incomplete for omitting essential structural cooperative relationships of elements.

Claims 34 and 43 have been amended to indicate, as the Examiner recommended, that the fiber protein of the CRAd is a chimeric fiber protein comprising the hAd3 or the Cad2 fiber knob domain, respectively, and that CRAd contains and expresses a nucleotide sequence encoding the chimeric fiber protein. Specifically, claim 34 beginning at line 6 recites in part: the hAd5 contains and expresses a nucleotide sequence encoding a fiber knob domain from an adenovirus subtype 3. Furthermore, claim 43 beginning at line 6 recites in part: the hAd5 contains and expresses a nucleotide sequence encoding the fiber knob domain of the canine adenovirus type 2.

It is respectfully submitted that the rejection is moot.

Accordingly, reconsideration and withdrawal of the rejection of claims 34-44 under 35 U.S.C. §112, second paragraph is respectfully requested.

As to the rejection of claims 34-44 under 35 U.S.C. §112, the Office Action asserts that the omitted element(s) is the adenoviral sequence(s) to which the VEGF promoter region or the CXCR4 or survivin promoters are operably linked such that the adenovirus replicates more efficiently in tumor cells than in most normal cells.

Applicant believes that the amendments made herein to the claims render this objection moot. Specifically, lines 11-14 of claim 34 recite that "the modified conditionally replicative adenovirus contains a deletion of the E1A promoter, and insertion of a promoter region selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or

survivin, such that replication is more efficient in tumor cells than in most normal cell types. Furthermore, lines 12-16 of claim 43 recite that "the modified conditionally replicative adenovirus contains a deletion of the E1A promoter, and insertion of a tumor-specific promoter from a gene encoding a protein selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin, such that replication is more efficient in tumor cells than in most normal cell types.

It is respectfully submitted that the rejection is moot.

Accordingly, reconsideration and withdrawal of the rejection of claims 34-44 under 35 U.S.C. §112, second paragraph is respectfully requested.

VI. The Rejections Under 35 U.S.C. §102 Are Overcome

Claims 25, 26, 28, 29, 34, 35, and 39 are rejected under 35 U.S.C. §102(a) as being anticipated by Takayama et al. as evidenced by Curiel et al. (WO 00/67576). Claims 25, 26, 28, and 31 are rejected under 35 U.S.C. §102(b) as being anticipated by Curiel, D.T. (Abstract 3287), as evidenced by Curiel, et al. (WO 00/67576).

Applicants respectfully disagree and traverse the rejections.

Initially, it is respectfully pointed out that for a Section 102 rejection to stand, the single prior art reference must contain all of the elements of the claimed invention, *see Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987), and, the single prior art reference must contain an enabling disclosure, *see Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest or enable Applicants' invention.

Turning first to the rejection of claims 25, 26, 28, 29, 34, 35, and 39 are directed to an infectivity-enhanced CRAd, containing a modified fiber protein, and a tumor-specific promoter, it is respectfully asserted that the rejection must fail. Takayama involves the use of CRAd in which the expression of E1 is controlled by the human VEGF promoter. Applicants respectfully direct the Examiner's attention to the fact that Takayama does not contain an enabling

disclosure. Curiel (WO 00/67576) cannot be said to cure this defect. Curiel (WO 00/67576) involves the genetic introduction of an RGD sequence in the fiber of a CRAd, allowing CAR-independent infection that leads to the enhancement of viral propagation and oncolytic effect. Moreover, Curiel (WO 00/67576) involves adenoviral vectors that either contain an E1A mutation or have a deletion of E1A, thus the CRAd vectors maintain of the native Ad promoters. On the other hand, the present invention involves adenoviral vectors wherein viral replication is controlled by substituting the E1A viral promoter, with a tumor associated-antigen promoter such as VEGF, CXCR4, or survivin. Curiel (WO 00/67576) does NOT relate to CRAd consisting of E1 under the control of VEGF, CXCR4, or survivin.

Accordingly, reconsideration and withdrawal of the rejection of claims 25, 26, 28, 29, 34, 35, and 39 under 35 U.S.C. §102(a) as being anticipated by Takayama et al. as evidenced by Curiel et al. (WO 00/67576) is respectfully requested.

Turning to the rejection of claims 25, 26, 28, and 31 under 35 U.S.C. §102(b) as being anticipated by Curiel, D.T. (Abstract 3287), as evidenced by Curiel, et al. (WO 00/67576), it is again respectfully asserted that the rejection cannot stand. Curiel (Abstract 3287) does not contain an enabling disclosure. And, for the same reasons as discussed above, Curiel (WO 00/67576) cannot be said to cure this defect. Curiel (WO 00/67576) involves the genetic introduction of an RGD sequence in the fiber of a CRAd, allowing CAR-independent infection that leads to the enhancement of viral propagation and oncolytic effect. Moreover, Curiel (WO 00/67576) involves adenoviral vectors that either contain an E1A mutation or have a deletion of E1A, thus the CRAd vectors maintain of the native Ad promoters. On the other hand, the present invention involves adenoviral vectors wherein viral replication is controlled by substituting the E1A viral promoter, with a tumor associated-antigen promoter such as VEGF, CXCR4, or survivin. Curiel (WO 00/67576) does NOT relate to CRAd consisting of E1 under the control of VEGF, CXCR4, or survivin.

Accordingly, reconsideration and withdrawal of the rejection of claims 25, 26, 28, and 31 are rejected under 35 U.S.C. §102(b) as being anticipated by Curiel, D.T. (Abstract 3287), as evidenced by Curiel, et al. (WO 00/67576), is respectfully requested.

VII. The Rejections Under 35 U.S.C. §103 Are Overcome

Claims 25-27, 30-32, 34, and 39-42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Takayama et al. (Abstract 1089), in view of Curiel et al. (WO 00/67576).

Claims 25-27, 30-32, 34, and 39-42, are rejected under 35 U.S.C. §103(a) as being unpatentable over Curiel (Abstract 3287) in view of Curiel (WO 00/67576). Claims 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Molnar-Kimber, WO 01/23004 in view of Curiel, et al., WO 00/67576. Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. (Abstract 1089), as evidenced by Curiel et al., (WO 00/67576), as applied to claims 25, 26, 28, 29, 34, 35, and 39, and further in view of Takayama et al., (Abstract 821).

Applicants respectfully disagree. The cited references do not render the instant invention obvious. The rejections are collectively addressed and respectfully traversed.

Establishing a *prima facie* case of obviousness requires three basic criteria: there must be some suggestion or motivation in the cited art to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references must teach or suggest all the claim limitations. MPEP 2143.

It is also well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, BOTH the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), i.e., "obvious to try" is <u>not</u> the test.

In this case, Takayama (Abstract 1089) allegedly involves the use of VEGF promoter-based CRAds further modified to express Ad3 in the knob domain of the fiber protein, for the treatment of lung cancer. This reference further investigates the synernergistic anticancer effect by co-infection of CRAd and non-replicative AdCMVTK containing HSV tyrosine kinase gene.

Curiel (WO 00/76576) allegedly involves the genetic introduction of an RGD sequence in the fiber of a CRAd, allowing CAR-independent infection that leads to the enhancement of viral propagation and oncolytic effect. Furthermore, Curiel (WO 00/67576) allegedly involves

adenoviral vectors that either contain an E1A mutation or have a deletion of E1A, such that the vectors are nonreplicative. The Examiner asserts that it would have been obvious at the time the invention was made t o have modified the fiber of the CRAd of Takayama (Abstract 1089) by insertion of an RGD peptide into the HI loop, rather than the replacement of the fiber knob, since Curiel taught that such a modification of a CRAd was useful for treating cancer, and including the tk gene in the CRAd would increase convenience of administration as well as the rate of co-transfection.

Curiel (Abstract 3287) allegedly generally describes CRAd for use in treatment of cancer comprising a fiber modified by insertion of RGD in the HI loop or by replacement with the knob of another subtype of adenovirus, wherein the E1 region of the CRAd is placed under control of a tumor specific promoter and may contain a therapeutic gene. As the Examiner noted, this reference does not teach insertion of an RGD-containing peptide into the HI loop. It also fails to teach inclusion of the HSV tk gene in the CRAd.

Molnar-Kimber allegedly teaches CRAds comprising an E1A gene under control of a tumor specific promoter that may also contain a therapeutic gene. As the Examiner points out, this reference does NOT teach to modify the adenoviral fiber either by insertion of an RGD peptide into the HI loop or by replacing the knob with that of a different adenovirus.

Takayama (Abstract 821) allegedly teaches a method of cancer treatment with an hAd5 vector having a VEGF promoter controlling its replication by operable linkage to the E1 region and a chimeric fiber protein with the knob domain of Ad3.

Applicants assert that none of the references, either alone or in any combination, teach or suggest the present invention, which is directed to an infectivity-enhanced conditionally replicative adenovirus having a fiber protein, modified either by insertion of an Arg-Gly-Asp containing peptide in the HI loop of the fiber protein, or by replacement of its fiber knob domain with a fiber knob domain from a different subtype of adenovirus AND which contains a tumor-specific promoter from a gene encoding a protein selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin operably linked to one or more early genes selected from the group consisting of E1, E2 and E4.

Specifically, none of the cited references teach or suggest the use of the following promoters: CXCR4 or survivin. The Examiner is respectfully invited to review the MPEP

MPEP 2143.03 stating in part that "To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)".

Applicant reminds the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicant believes that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. There is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

VIII. The Double Patenting Rejection Is Overcome

Claims 25-42 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-3 and 9-12 of U.S. Patent No. 6,824,771 in view of Curiel et al., WO 00/67576; Takayama et al. (Abstract 1089); and Takayama et al. (Abstract 821).

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to the copending Application No. 10/697,535 will be filed for the purposes of expediting prosecution.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner is respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks, amendments and Declaration, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
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